

**EXHIBIT VI**

**NDA SUBMISSION LETTER**

# SCHERING CORPORATION

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December 27, 2001

David Orloff, M.D., Director,  
Division of Metabolic and Endocrine Drug Products      **NDA 21-445**  
Food and Drug Administration      **ZETIA (ezetimibe) TABLETS**  
Center for Drug Evaluation and Research  
HFD-510, Room 14B-19  
5600 Fishers Lane  
Rockville, MD 20857

## **SUBJECT: ORIGINAL NEW DRUG APPLICATION**

Dear Dr. Orloff:

Per 21 CFR 314.50, submitted on behalf of the MSP Singapore Co. LLC, a joint venture between Merck & Co., Inc. and Schering Corporation, is an original New Drug Application for ZETIA™(ezetimibe) tablets for the treatment of:

- primary hypercholesterolemia (heterozygous familial and non-familial), when administered alone or with an HMG-CoA reductase inhibitor, as an adjunct to diet and exercise;
- hypercholesterolemia in patients with homozygous familial hypercholesterolemia (HoFH), as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable, and
- elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.

### **Request and Justification for Priority Review**

We herein request a priority review based upon clinically important results obtained from our trials in HoFH and homozygous sitosterolemia, two rare forms of dyslipidemia which share grim prognoses in terms of the development of premature atherosclerosis, myocardial infarction, and coronary heart disease death.

Current therapeutic management of these diseases is sub-optimal. While there is no approved pharmacological therapy for sitosterolemia, current standard therapy for HoFH (LDL apheresis and high-dose statin administration) is often inadequate.

Therefore, ezetimibe is a new or alternative therapeutic option for these serious diseases in two populations with unmet medical needs.

As detailed in this application, ezetimibe offers added clinical benefit over other interventions for the proposed indications from both an efficacy and safety standpoint. It is the opinion of the MSP Singapore Co. LLC that treatment with ezetimibe is a significant therapeutic advance in the treatment of HoFH and homozygous sitosterolemia.

#### *Homozygous familial hypercholesterolemia*

HoFH is a rare, autosomal dominant inherited disorder caused by mutations of the gene encoding the LDL receptor. Patients with HoFH have abnormalities in both LDL receptor alleles resulting in markedly elevated low-density-lipoprotein-cholesterol (LDL-C) levels and development of severe and premature atherosclerosis. HoFH is a rare condition with a frequency of approximately one in a million individuals. Historically, most HoFH patients die from accelerated coronary heart disease (CHD) by the fourth decade of life, some before reaching adulthood.

HoFH remains a challenging disease to treat despite current pharmacological and non-pharmacological interventions. Current standard therapy for HoFH combines LDL apheresis and high-dose HMG-CoA reductase inhibitor (statin) administration. LDL apheresis, where available, requires frequent treatments and may not fully control LDL-C levels. Unlike patients with heterozygous FH in which the remaining normal LDL receptor allele can be upregulated to some extent, HoFH patients show only modest response to statins. The large majority of HoFH patients fail to achieve optimal reduction of LDL-C through existing therapies. Treatment of HoFH with ezetimibe will therefore provide a new therapeutic option for an unmet medical need.

#### *Overview of study P01030*

The results demonstrate that ezetimibe coadministered with statins (40/80 mg or 80 mg only) reduced LDL-C from baseline to endpoint significantly more than treatment with statin at maximal doses (80 mg).

- The difference in mean percent change from baseline to endpoint in direct LDL-C in the ezetimibe/statin (40/80) group relative to the statin 80 mg group was -14.1% ( $p<0.001$ ) and,
- A greater difference (-20.5%) was observed in the ezetimibe/statin (80 mg only) group relative to statin (80 mg) alone ( $p<0.001$ ). In particular, this comparison provides the best estimate of an ezetimibe-attributable effect, since the patients in both of these groups were receiving the maximal (80 mg) statin dose.

Ezetimibe coadministered with atorvastatin or simvastatin at doses of either 40 or 80 mg daily was well tolerated and had a safety profile similar to that of patients administered 80 mg of these statins alone.

A final report of this study is found in section 8.D of this NDA.

*Homozygous sitosterolemia*

Homozygous sitosterolemia (phytosterolemia) is a rare autosomal recessive disorder that is characterized by the accumulation of plant sterols and 5 $\alpha$ -saturated stanols in plasma and tissues. Affected individuals are at high risk for premature atherosclerosis and fatal myocardial infarction. The principal metabolic aberrations are increased absorption and reduced biliary excretion of plant sterols.

Treatment of homozygous sitosterolemia is an unmet medical need. Current treatment options are limited to the restriction of dietary plant sterol intake and the facilitation of bile acid malabsorption through the off-label use of bile-acid sequestrants or ileal-bypass surgery. Statins are generally ineffective. There is currently no FDA approved therapy for this disorder. Rigorous adherence to these treatments can lead to reductions in plasma levels and tissue pools of plant sterols in patients with sitosterolemia, but invariably does not adequately correct the biochemical abnormalities or eliminate the increased disease risk. Moreover, these treatments are difficult to maintain due to the poor palatability of the diet and the gastrointestinal side effects of bile-acid sequestrants.

*Overview of study P02243*

The final report of this study is found in section 8.D of this NDA. Briefly, our results demonstrate that ezetimibe reduced plasma sitosterol and campesterol concentrations from baseline -21.0 and -24.3% ( $p<0.01$ ), respectively. Ezetimibe-treated subjects, concurrently using bile-acid-binding resins, had a mean change in plasma sitosterol concentrations of -20.4%. These reductions in plasma concentrations of plant sterols exhibited a decreasing trend throughout the entire study period, suggesting that greater reductions may occur with longer treatment periods.

Ezetimibe was well tolerated and safe in this patient population. These results indicate that ezetimibe is an effective agent for the treatment of homozygous sitosterolemia, thus, addressing an unmet need in this high-risk patient population.

Overall, 4032 subjects received ezetimibe in the Phase II and III clinical program. Of these, 1735 received ezetimibe 10 mg as monotherapy and 2297 received ezetimibe coadministered with a statin. Generally, treatment with ezetimibe was well tolerated, both as monotherapy and when coadministered with statins. Treatment with ezetimibe, whether as monotherapy or coadministered with a statin, was not associated with an increased risk of muscle toxicity.

### General

Merck & Co, Inc and Schering Corp. entered into a joint venture for the development of ezetimibe. In doing so, the MSP Singapore Co LLC was formed, and on October 26, 2000 (serial no.106) Schering Corporation (original Sponsor) transferred IND 52,791 to the MSP Singapore Co. LLC with Schering Corporation acting as agent. Representatives from both Merck and Schering contribute to the joint venture. Both Merck and Schering have conducted studies on behalf of the MSP Singapore Co.

### Pre-NDA Discussions

The clinical content and format of this application were discussed with the Division of Endocrine and Metabolic Drug Products at the April 25, 2001 pre-NDA meeting. This application is consistent with that described in the briefing book of April 3, 2001 (serial no.143).

Subsequent to the pre-NDA meeting, a number of discussions with the Agency have occurred. The applicant submitted to the IND a request for clarification of the Agency's minutes on August 21, 2001 (serial no.189). These included acknowledgement that a bioavailability (BA) study comparing tablet and solution formulations was discussed though Merck/Schering did not agree to conduct this study at the meeting. In a November 21, 2001 discussion, Mr. William Koch acknowledged this clarification and noted that the lack of a BA study would not be fileability issue.

A proposal regarding the content of the electronic datasets was forwarded to Mr. William Koch on June 25, 2001. As requested, the applicant submitted on August 6, 2001 (serial no. 182) a derived dataset from one of the monotherapy studies for review by the statistical reviewer. Our plan was found acceptable with general comments on the sample dataset made by Ms. Joy Mele on August 23, 2001. The applicant acknowledges that Dr. Japo Choudhury, the new statistical reviewer assigned to the submission, may request additional information after submission.

Teleconferences occurred with the Division on September 6 and 23, 2001 to discuss the Integrated Summaries of Safety and Efficacy. The applicant submitted to the Agency their understanding of the September 6 discussion on October 5, 2001 (serial no. 182). Notably, the applicant agreed to provide approximately 2 weeks after the NDA submission, a document (reviewer aid) outlining the significance test used for screening adverse event data.

The applicant believes that this application is consistent with both the discussions held and agreements made with the Agency from the End of Phase II and pre-NDA meetings and all subsequent teleconferences.

### Tradename

ZETIA™, the proposed tradename for ezetimibe, was submitted for OPDRA review to IND 52,791 on November 19, 2001 (serial no. 209).

### **Chemistry, Manufacturing and Controls (CMC) Information**

The following summarizes the key Chemistry, Manufacturing and Controls (CMC) issues discussed with the Division throughout the development program:

#### *Drug Substance Manufacture*

At the CMC End of Phase II (EOPII) meeting held October 20, 1999, agreement with the Division was reached concerning the designation of 4'-Fluoro-5-oxobenzenepentanoic acid (Compound I) and 4-[[4-Fluorophenyl]imino]methylphenol (Compound VII) as Starting Materials. The chemistry used to manufacture the Starting Materials is provided in the application (Section 4A4) as requested by the Division at the pre-NDA CMC meeting held April 27, 2001. As the Division stipulated at this meeting, the application includes the control measures for the chiral catalyst used in the drug substance synthesis.

#### *Drug Substance Pseudomorphic Forms*

The ability of Ezetimibe to interconvert from an anhydrous to hydrous form was initially discussed with the Division at the EOPII meeting. At the pre-NDA CMC meeting, evidence was provided to support the position that there is no need to conduct a bioequivalence study for hydrated vs. anhydrous tablets. This was based on a demonstration of equivalent physicochemical properties of the two forms as well as comparable stability data generated on anhydrous tablets vs deliberately hydrated tablets. This understanding was documented in our summary of agreement slides generated at the close of the pre-NDA CMC meeting as well as in our meeting minutes submitted on May 9, 2001. However, the FDA pre-NDA CMC meeting minutes did not acknowledge agreement on this issue.

A request for clarification concerning FDA's pre-NDA CMC meeting minutes was submitted to the IND on July 25, 2001. Following several discussions with the FDA on this topic, a teleconference was held on October 12, 2001 with Drs. Ahn, Johnson and Mr. Koch from the Division. FDA's minutes, dated October 31, 2001, included a request that comparative dissolution profile data for hydrous and anhydrous forms of ezetimibe utilizing the medium agreed upon during the March 14, 2000 teleconference (0.45% SLS in 0.05M sodium acetate buffer pH 4.5) and an additional medium of our choice be provided in the NDA submission. The requested study has been conducted and the data demonstrate that the hydrous and anhydrous forms are comparable based on  $f_2$  values. These data were submitted on December 17, 2001 to IND 52791 (Serial No. 216). We hereby cross-refer to IND 52791, Serial No. 216 to fulfill FDA's request for additional dissolution data. Based on these confirmatory data, the Division will not require a PK study as stated in their minutes of October 31, 2001.

#### *Specifications for Drug Substance and Drug Product*

The proposed testing regimens for drug substance and drug product were reviewed with the Division at the pre-NDA CMC meeting. Several points should be noted: The Division concurred that a specification for the water content as determined by Karl Fischer is acceptable as a control for the hydrate level. As requested by the

Division, data correlating the moisture content to hydrate level are included in Physicochemical Characterization of SCH 58235 (Section 4A1) of the NDA. In addition, specifications for the keto compound (SCH 57871) and Total Unspecified impurities/degradants have been added to both the drug substance and drug product specifications as requested by the Division.

There were several communications with the Division regarding specifications for Particle Size Distribution for Ezetimibe. We refer you to the July 31, 2001 teleconference with Drs. Qiu, Moore, Wei and Mr. Koch of the Division, wherein it was agreed that a three point definition (median, % $<3\mu\text{m}$ , and % $<10\mu\text{m}$ ) of the particle size distribution was appropriate. The rationale for the specification is provided in Section 4A7 of this application.

At the EOPII meeting, the Division requested that bioburden testing be conducted on the drug product to determine if testing would be required routinely. Accordingly, the results of Microbial Limits testing for drug substance and drug product are provided in Sections 4A7 and 4B8, respectively.

#### *Stability Data for Drug Substance and Drug Product*

The registration stability programs for drug substance and drug product were discussed with the Division at the EOPII meeting at which time we presented a review of the changes in the drug substance and drug product methods of manufacture throughout the development program. As agreed with the Division, we are including drug substance stability data (Section 4A8) for three batches manufactured at Schering-Plough Union NJ by the Final Synthesis Process Version 2 (Borane-Dimethylsulfide in Stage 2 and TBME in Stage 4) and 1 Union batch manufactured by Final Synthesis Final Process (Borane-Tetrahydrofuran in Stage 2 and TBME in Stage 4). Drug substance stability data are provided for two additional batches prepared by the Final Synthesis Final Process, one of which was manufactured at the proposed commercial site (Schering-Plough Singapore).

The drug product stability data presented in the application include three primary stability batches manufactured at Schering-Plough Kenilworth, NJ and two production-scale, site-specific stability batches manufactured at the proposed commercial site, Schering-Plough Las Piedras Operations, using two equipment trains. Results of additional drug product stability studies are also provided in Section 4B8. The drug product stability program included a bracketing protocol as agreed to by the Division at the EOPII meeting. It was agreed at the pre-NDA CMC meeting that the amount of stability data generated are sufficient to support filing the NDA (refer to FDA Meeting Minutes Addendum dated 11/20/01). Subsequent to the pre-NDA meeting, a request for guidance was submitted to IND 52791 (Serial No. 192, August 30, 2001) regarding a change in proposed fill size from a 100 count bottle to a 90 count bottle with no change in container size or materials of product contact. The Division took no action on this amendment, from which we concluded that the Division agrees that our existing bracketing protocol supports 90 count bottles.

#### **Executed Batch Records for Drug Product**

As agreed with the Division at the pre-NDA CMC meeting, copies of executed drug product batch records are provided for one pilot scale primary stability batch (manufactured in Kenilworth NJ) and two commercial scale batches manufactured at Las Piedras Operations which are representative of each equipment train proposed in the application.

#### **Field Copy Certification**

As requested by the New Jersey Division, we are providing a copy of the cover letter only to the District because the product is manufactured outside of New Jersey. A true and complete copy of Section 4, Chemistry, Manufacturing and Controls Information is being sent to the San Juan District Office.

#### **Financial Disclosure**

In accordance with 21 CFR Part 54, FDA Forms 3454 and, where applicable, Forms 3455 are included with this application for both Schering Corporation and Merck & Co., Inc. As discussed with Dr. Linda Carter on December 5, 2001, it is acceptable to submit the Merck financial disclosure information in a sealed envelope in the section 19 of the NDA.

#### **Electronic Submission**

This submission is provided in hardcopy and electronic format as read-only electronic published (PDF) documents per the guidance, "*Providing Regulatory Submissions in Electronic Format - NDAs*" issued January 1999. Please note that Section 11 includes a folder containing the SAS programs for the statistical reviewer. Per request of the clinical pharmacology reviewer, SAS transport files for the blood concentration data are also included. The tumor incidence data from the oncogenicity studies are provided in SAS transport format in Section 5. Further details on the submission are attached in Appendix 1.

A sample CRF was submitted to Dr. Randy Levin for comment on May 4, 2001, and this was found acceptable.

In communications with Dr. Randy Levin and Mr. William Koch on November 16 and 26, 2001, the Agency agreed to accept SAS transport files up to a 50 MB size limit.

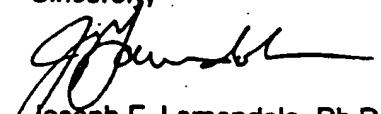
#### **Pediatric rule**

At the pre-NDA meeting of April 25, 2001, the Agency granted the applicant a deferral of pediatric data on patients  $\geq$  10 years of age and a waiver of pediatric data on patients  $\leq$  10 years of age.

A check in the amount of \$309,647 was sent to the FDA c/o Mellon Bank, Pittsburgh, PA on November 1, 2001. This check represented the estimated user fee amount for the current fiscal year as provided by the FDA. The user fee number is 4220.

Please be advised that the material and data contained in this submission are considered to be confidential. The legal protection of such confidential commercial material is claimed under the applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(j) as well as the FDA regulations.

Sincerely,



Joseph F. Lamendola, Ph.D.  
Vice President  
U.S. Regulatory Affairs

## **Electronic Submission Information**

### **Description Format (Electronic/Paper)**

The following identifies the primary sections included in this submission. Each section has been identified with an "X" if presented in paper or electronically. If a section is not included in this application, it has been removed from this list.

| <b>Item</b> | <b>Description</b>                          | <b>Electronic</b> | <b>Paper</b> |
|-------------|---|-------------------|--------------|
| 1           | Index                                       | X                 | X            |
| 2           | Labeling                                    | X                 | X            |
| 3           | Application Summary                         | X                 | X            |
| 4           | Chemistry                                   | X                 | X            |
| 5           | Nonclinical Pharmacology & Toxicology       | X                 | X            |
| 6           | Human Pharmacokinetics and Bioavailability  | X                 | X            |
| 8           | Clinical                                    | X                 | X            |
| 10          | Statistical*                                | X                 | X            |
| 11          | Case Report Tabulations                     | X                 | N/A          |
| 12          | Case Report Forms                           | X                 | N/A          |
| 13          | Patent Information                          | X                 | X            |
| 16          | Debarment Certification                     | X                 | X            |
| 17          | Field Copy Certification                    | X                 | X            |
| 18          | User Fee Cover Sheet                        | X                 | X            |
| 19          | Financial Information                       | N/A               | X            |
| 20          | Other – Claim for Exclusivity/Pediatric Use | X                 | X            |

\* This information is identical to Item 8.

### **Electronic Submission Summary**

**Media Type:** Digital Tape (DLT 20/40 written with NT 4.0 Backup)

**Number of Media:** 1 Digital Tape  
Electronic Submission & Toxicology/  
Preclinical/Clinical Data/Supporting Information

**File Formats:** Portable Document Format (PDF)  
SAS Transport Version 5 Format/SAS Version  
6.12 Efficacy Analysis Programs

**Total Size:** 5.03 GB

**Virus Verification:**

This is to certify that this electronic submission has been scanned for viruses using Intel LANDesk 95, version 5.0.

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**Guidance Deviations:**

**None**